

# Hepatitis C: Update on Testing and Treatment

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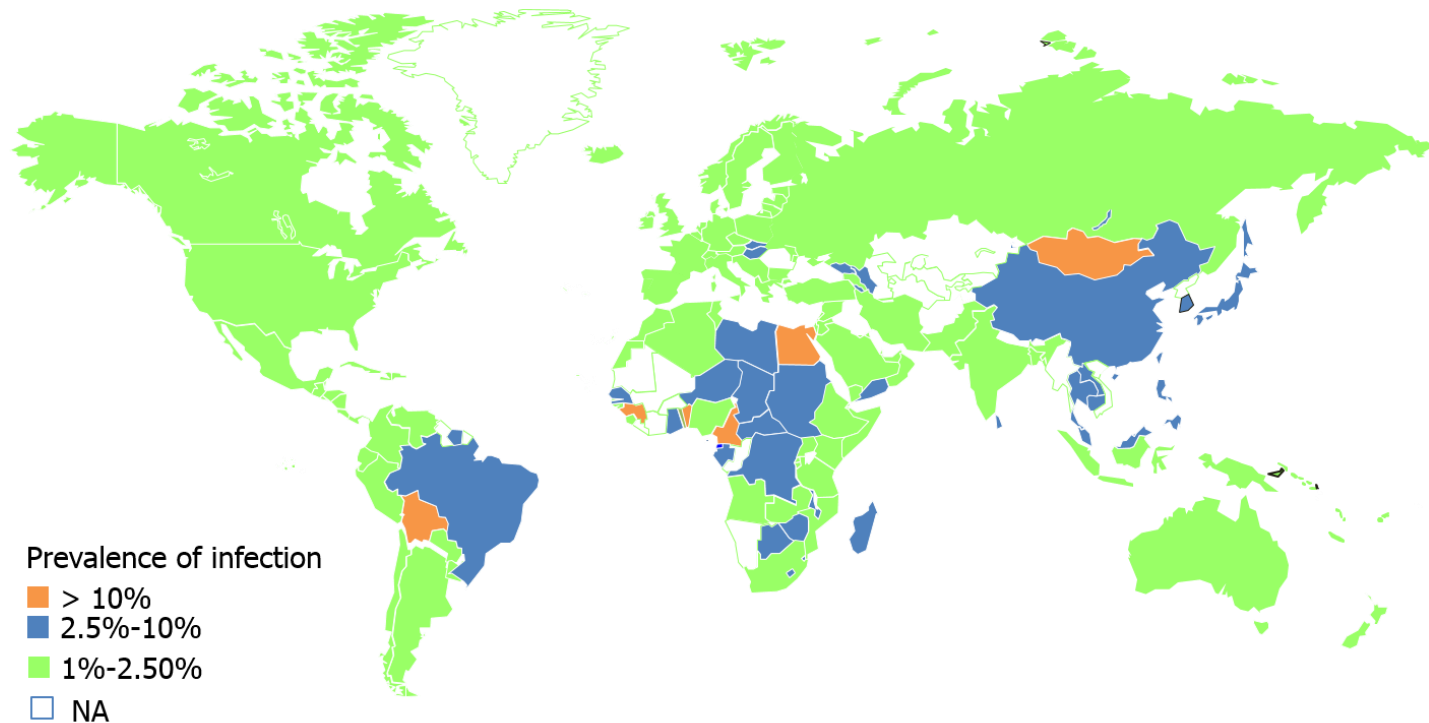
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# Learning Objectives

- Identify the recommended screening guidelines for Hepatitis C.
- Recognize who should be prioritized for Hepatitis C treatment.
- Describe the new paradigm for Hepatitis C treatment using all oral therapies.

# Hepatitis C is a Global Health Problem

- Estimated 170 million persons with HCV infection worldwide. World Health Organization 2008 (<http://www.who.int/ith/es/index.html>)

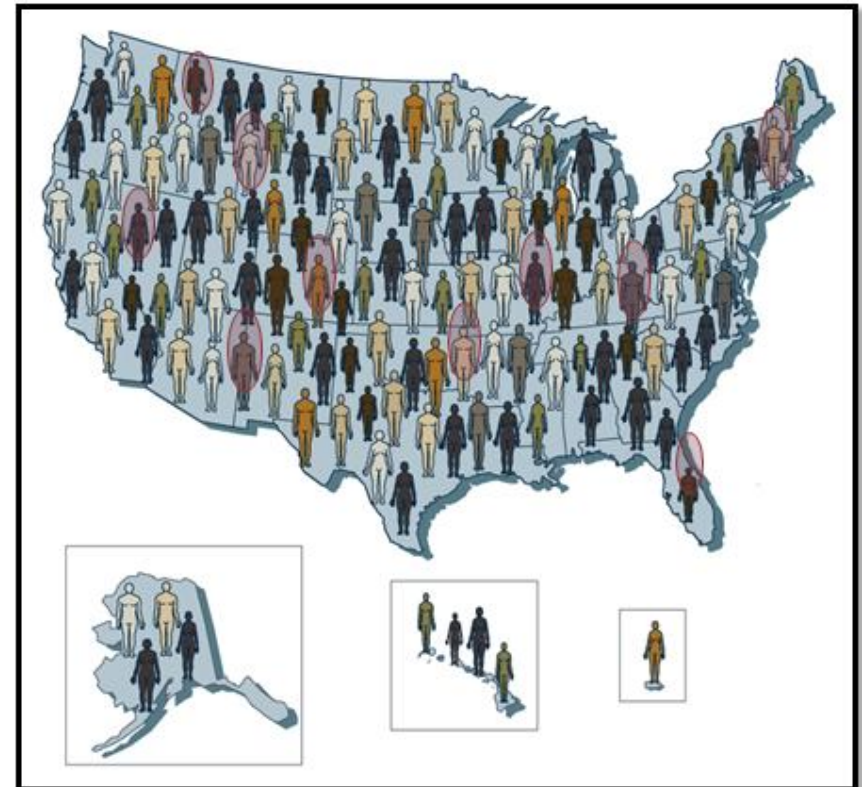


# Hepatitis C Prevalence (NHANES estimate)

- 3.2 Million HCV Antibody positive.
- Possibly up to 7.1 Million HCV Antibody positive in US.

Armstrong GL, et al. Ann Intern Med. 2006;144:705-14.;

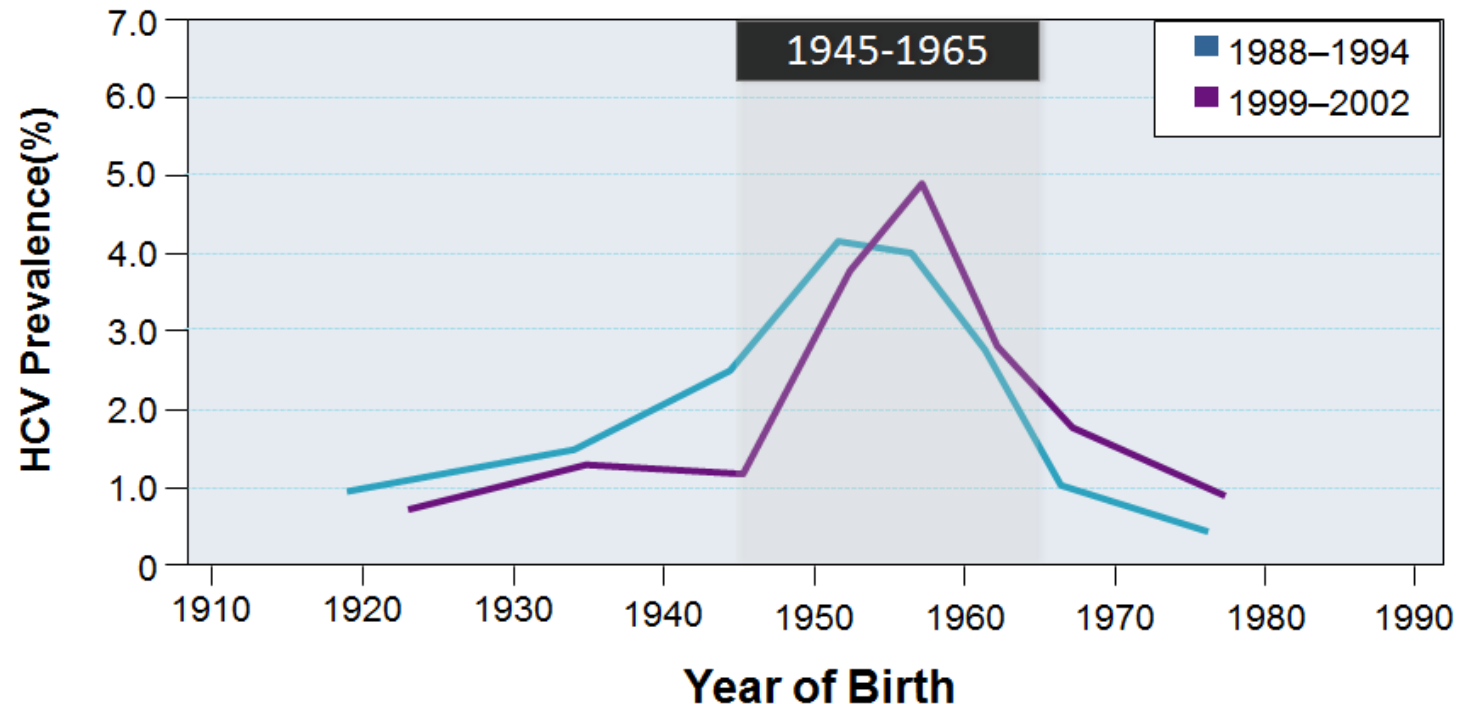
Chak E, et al. Liver Int. 2011;31:1090-1101



# Prevalence of HCV in Select Populations

- Incarcerated ~330,000-860,000 (16-41%).
- IVDU ~300,000 (80-90%).
- HIV infected ~300,000 (30%).
- Alcoholics ~240,000 (11-36%).
- Living below poverty level ~940,000 (2.4%).
- Homeless ~175,000 (22%).
- Veterans ~280,000 (8%).
- Children age 6-18 ~100,000 (.1%).

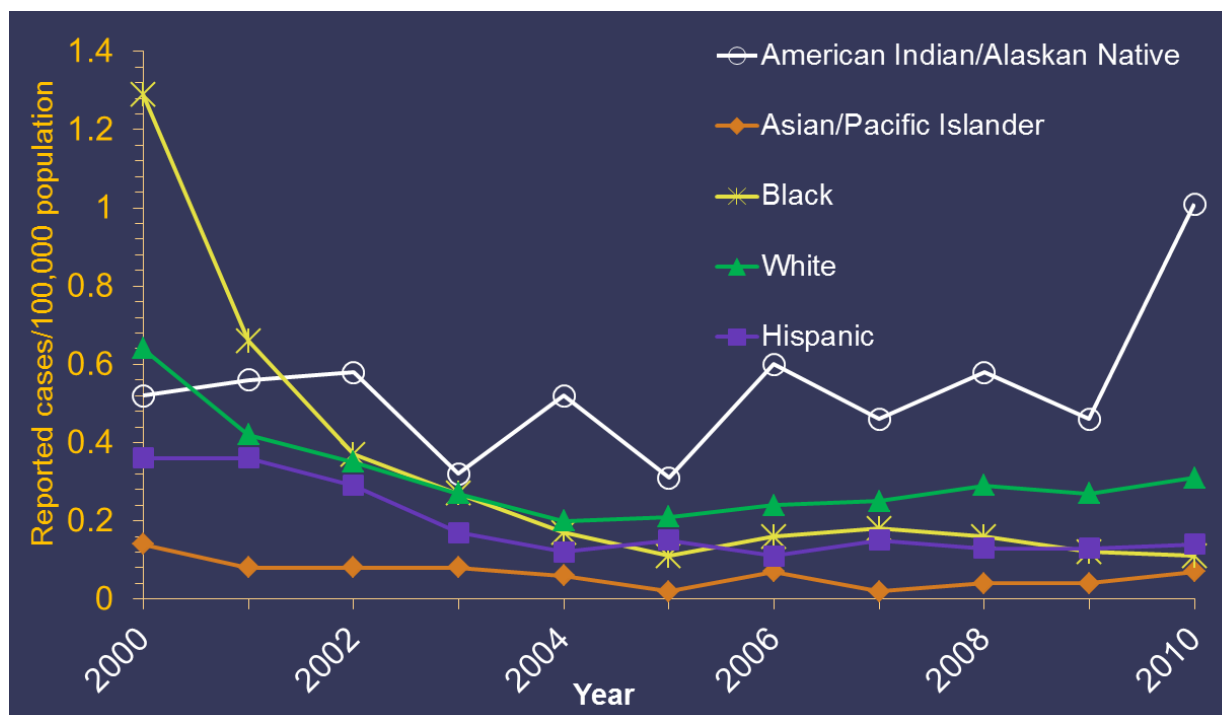
# Prevalence of HCV Antibody, by Year of Birth



- NHANES Survey: United States, 1988-1994 and 1999-2002.

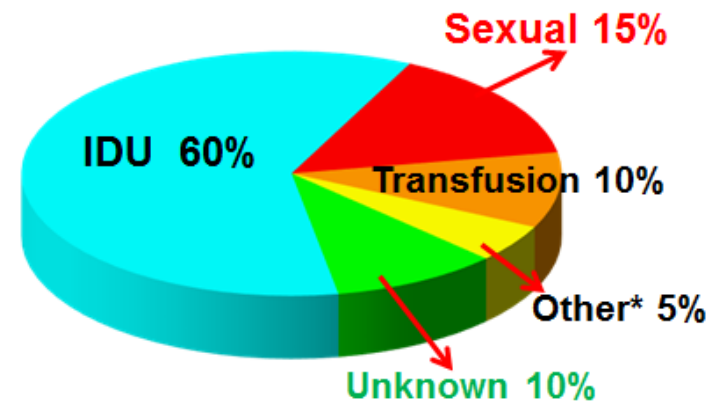
# Incidence of Acute Hepatitis C

By race/ethnicity — United States, 2000–2010



# HCV: Transmission

- Blood:
  - IDU is the leading cause in the United States
  - Blood transfusion (Before 1992)
  - Percutaneous injuries
- Sexual contact:
  - Rare in heterosexual
  - More frequent in MSM
- Mother-to-child:
  - Rate is 1.7% - 4.3 %



# HCV Transmission

- Many patients do not know they were exposed.
- Many patients were exposed and infected decades ago.
- For a proportion of patients, source of HCV infection cannot be determined.

# HCV household recommendations

- Do not share razors, toothbrushes, needles.
- No special precautions for sexual partners with discordant HCV status.
- No other precautions are necessary.

Who Should be Screened for  
HCV?

# Groups Recommended for HCV Testing by AASLD

- Recent/past injection drug users—even if only used once.
- Recipients of transfusion/transplantation before July 1992.
- Groups with high HCV prevalence: HIV-infected, Hemophiliacs, Hemodialysis recipients, Patients with unexplained AST/ALT elevations.
- Children born to women infected with HCV.
- Healthcare, public safety, and emergency medical personnel following needle injury or mucosal exposure to HCV-infected blood.
- Current sexual partners of individuals infected with HCV.

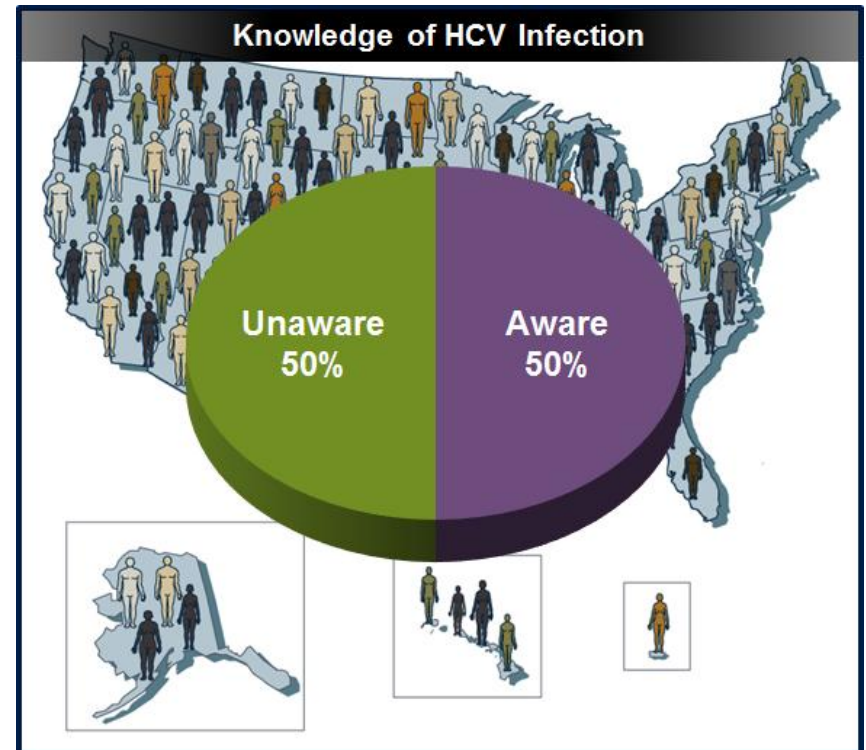
*Ghany MG, et al. Hepatology. 2009;49:1335-1374.*

*Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998;47:1-39.*

# Awareness of HCV Infection Status

- NHANES Survey, United States, 2001-2008.

*Source: Denniston M, et al.  
Hepatology. 2012;55:1652-61.*



# Rationale for Considering Birth Cohort Screening Recommendations

- 45%-85% of infected persons are undiagnosed.
- Limitations of current risk-based strategies.
- 75% of chronic infections are in persons born from 1945-1965.

# Recommendations

*Centers for Disease Control and Prevention*

**MMWR**

Morbidity and Mortality Weekly Report

Recommendations and Reports / Vol. 61 / No. 4

August 17, 2012

## Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965



# Screening for HCV infection in Adults: USPSTF Recommendations

- Released June 24, 2013.
- USPSTF Grade B recommendation:
  - Adults at high risk.
  - Adults born 1945-1965.
- Grade B:
  - Co-pay support (ACA).
  - Priority for performance measures.
- Consistent with CDC recommendations.

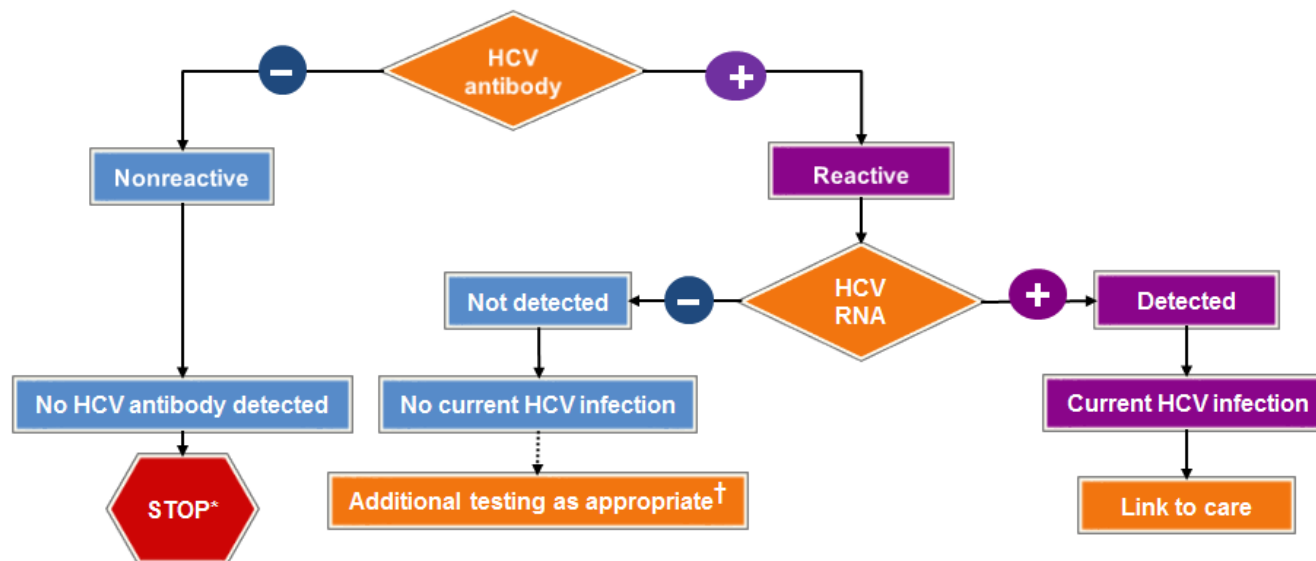
# IHS HCV Screening

- Developmental GPRA measure since 2011.
- Cumulative measure (screened once ever).
- Screening rates have tripled to approximately 30% of birth cohort screened in federal sites.
- Leading Service Units have already completed >50% screening.

# IHS HCV Screening – Birth Cohort

- Leading sites doing one or more of the following:
  - Use of HCV screening reminder in EHR.
  - Standing protocol/order for HCV screening.
  - Delegate screening away from provider (usually nurses).

# Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection



Source: CDC. *Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR.* 2013;62(18).

\* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

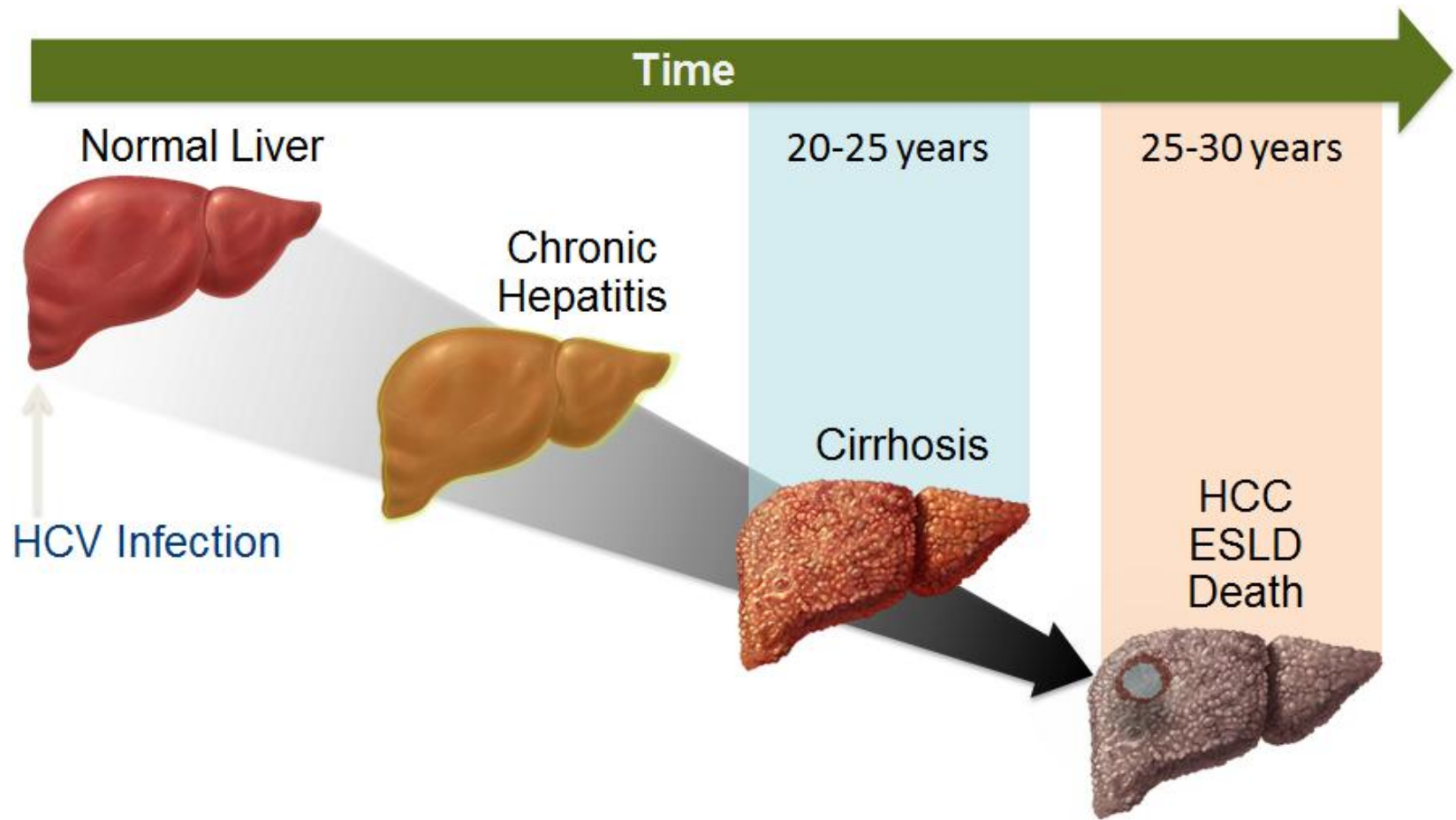
† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Slide courtesy AASLD Curriculum & Training

# Management of Patients with Positive HCV Antibody and Undetectable HCV RNA

- If patient previously treated for HCV, this indicates cure:
  - No need for repeat HCV-RNA testing.
  - Does not imply immunity to HCV.
- If liver function tests abnormal:
  - Evaluate for other causes of liver disease.
  - If suspect acute HCV or recent exposure, repeat HCV RNA within 6 months.

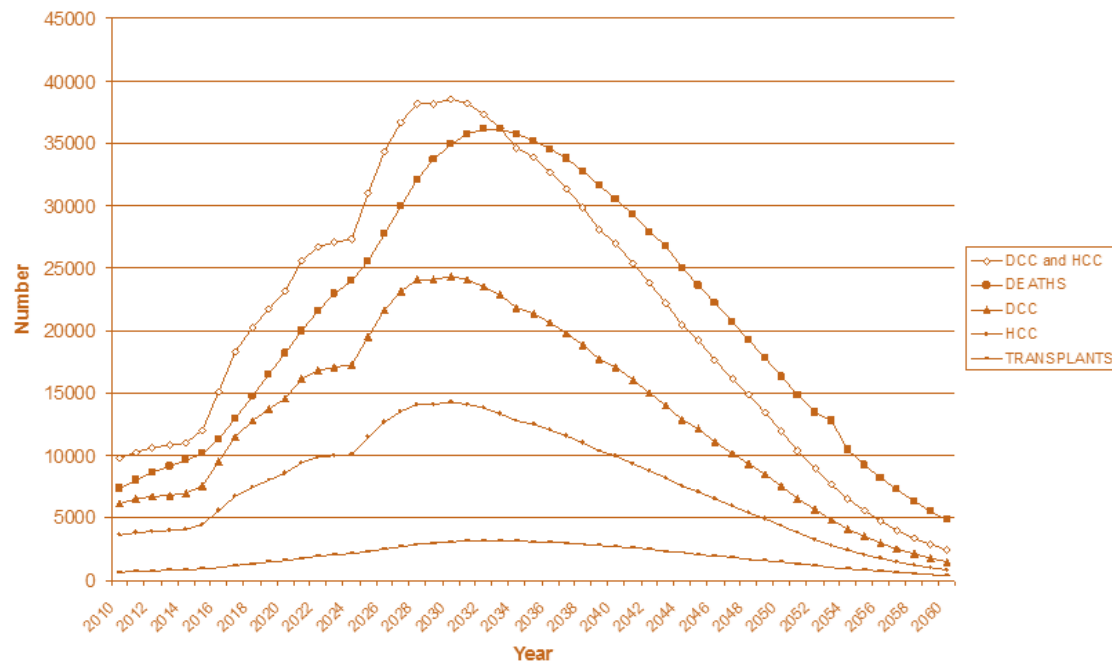
# Hepatitis C: Progression of Disease



# The Approaching Storm

- Long-Term Consequences of Untreated HCV.

# Forecasted Annual Incident Cases



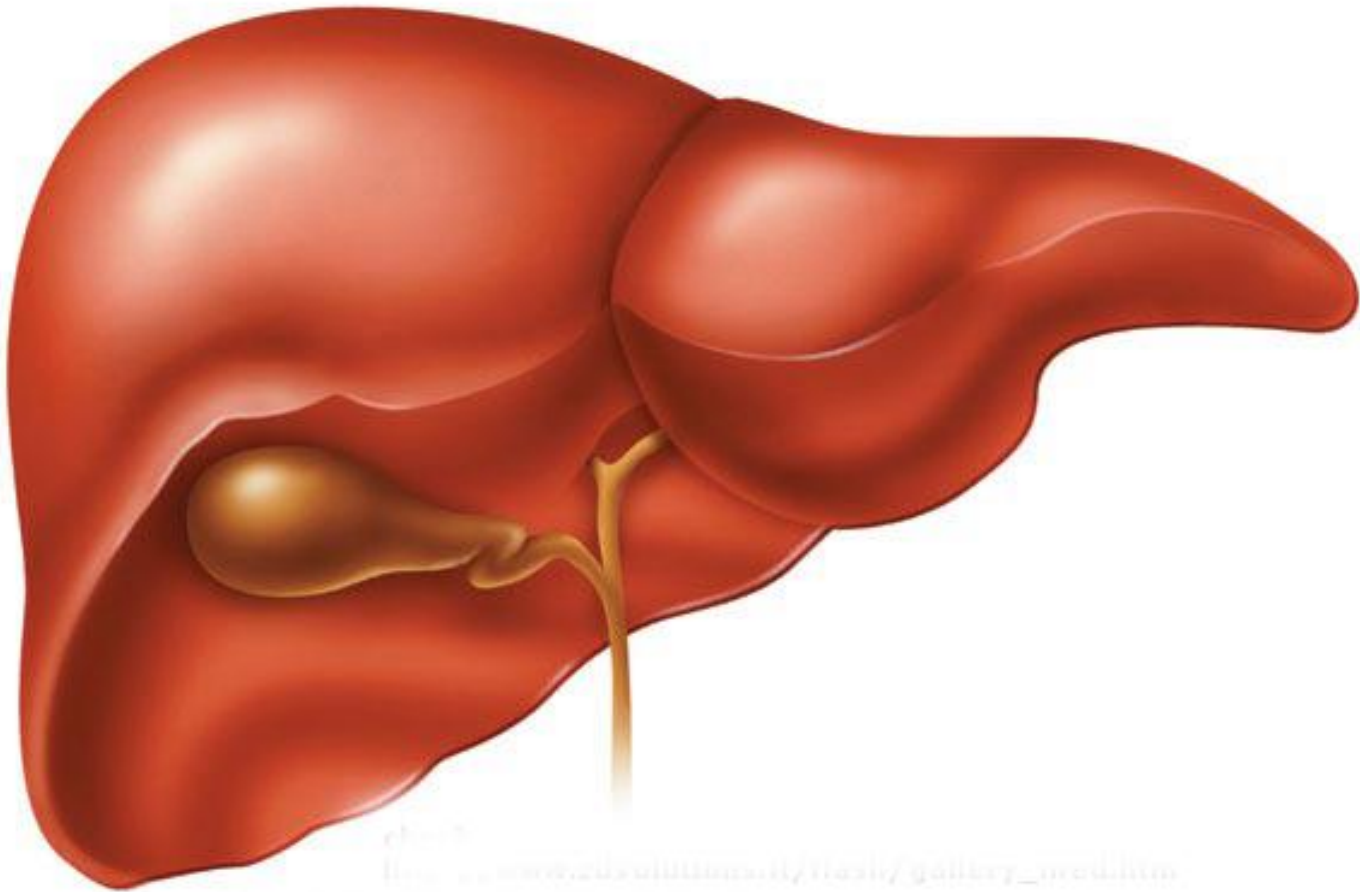
Forecasted Annual Incident Cases of Decompensated Cirrhosis (DCC), Hepatocellular Carcinoma (HCC), Liver Transplants, and Deaths Associated with Persons with Chronic Hepatitis C Infection and No Liver Cirrhosis in the United States in 2005

*Rein, DB, Wittenborn, JS, Weinbaum, CM Sabin, M, Smith, BD, Lesesne, SB. Forecasting the Mortality and Morbidity Associated with Prevalent Cases of Pre-Cirrhotic Chronic Hepatitis C Infections in the United States. Journal of Digestive Liver Diseases 2010.*

# Progression of Disease

- Disease progression is variable and non-linear.
- Modifiable factors are important in disease progression and should be addressed:
  - Weight loss.
  - Diabetes control.
  - Alcohol and marijuana.

# HCV is not just a Liver Disease



Downloaded from [www.resolution.com/vlax/gallery\\_med.htm](http://www.resolution.com/vlax/gallery_med.htm)

# Common Symptoms of HCV in the Absence of Cirrhosis

- Fatigue.
- Impaired cognitive function (brain fog).
- Migratory arthralgia or myalgia.
- Depression.

# Extrahepatic Manifestations (1)

- Approximately 40% of HCV patients will develop at least one extrahepatic manifestation.
- Often not clinically recognized.
- Many patients may not have concurrent evidence of liver disease.

# Extrahepatic Manifestations (2)

- Renal Disease.
- Neuropathy.
- Dermatologic Manifestations.
- Diabetes.
- Lymphomas.

# Porphyria Cutanea Tarda (PCT)



# Diabetes

- Risk increased by 70% compared to non-infected controls (OR 1.7).
- Successful HCV treatment associated with decrease in insulin resistance and reduction in incidence of diabetes mellitus.

*White DL, et al. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. Hepatol. 2008;49(5):831.*

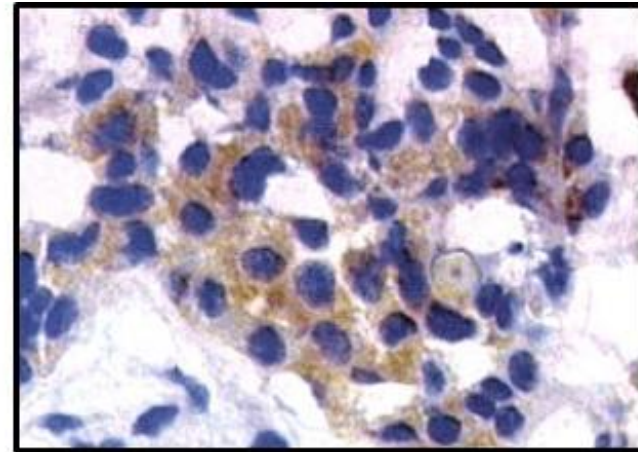
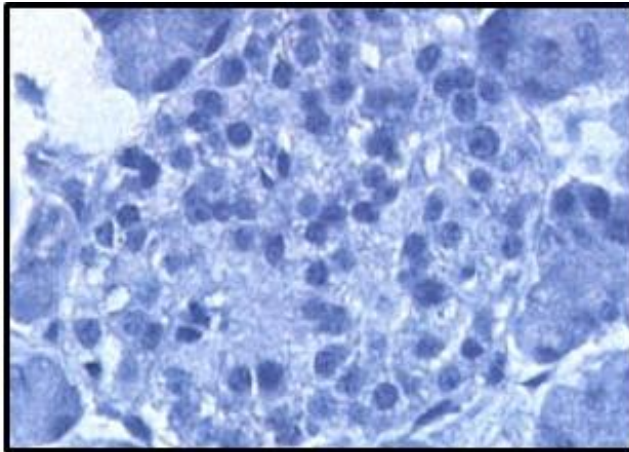
Why does HCV increase the risk  
for DM?

# Direct effects of HCV on DM risk

- Pancreatic islet cell infection:
- 39% of pancreatic islets infected
- +Evidence of  $\beta$ -cell dysregulation

Masini et al. *Diabetes Care* 2005.

Control



HCV+

# Effects of DM on HCV Infection

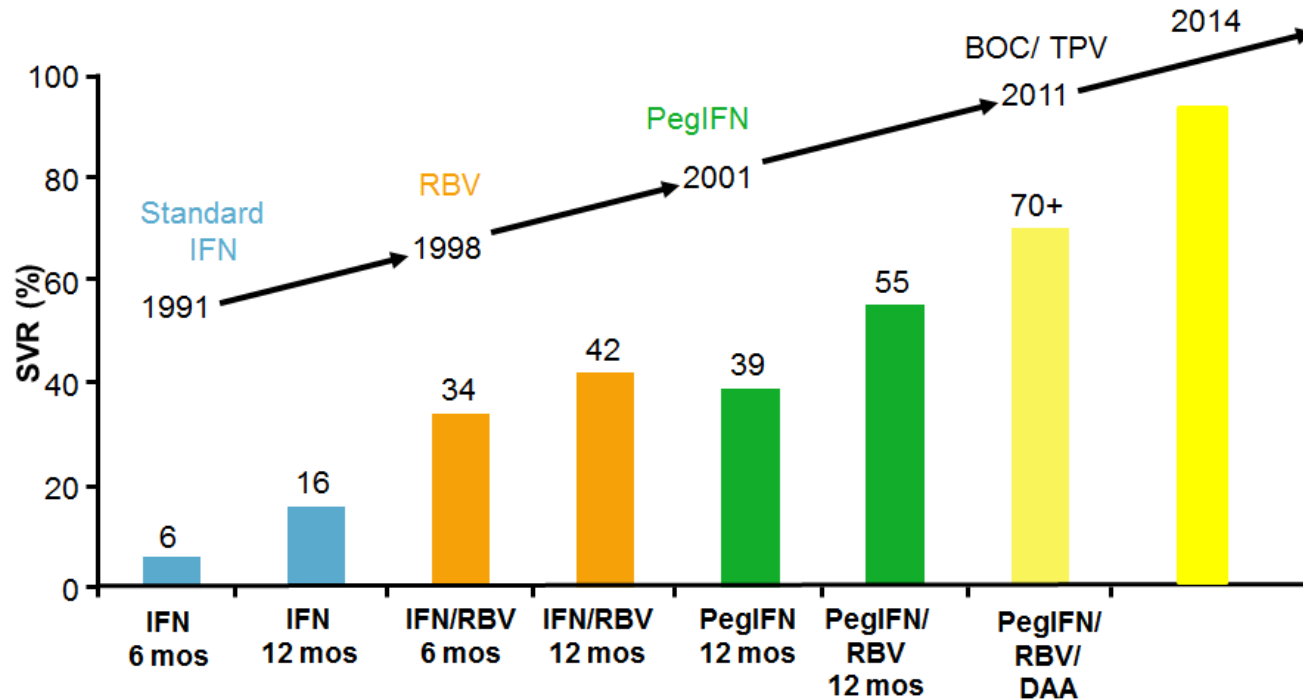
- Exacerbates progression of liver disease
- Reduces efficacy of HCV treatment
- Increases risk of HCC by 70%

*Hui et al. Gastroenterology 2003. / Romero-Gomez et al. Hepatology 2008.  
Arase et al. Hepatology 2013. / Tseng et al. Diabetes Metab Res Rev 2013.*

# Extrahepatic Manifestations (3)

- Patients with extrahepatic manifestations should be prioritized for treatment.
- Successful treatment of HCV reduces risk of DM and lymphoma.
- Successful treatment of HCV has benefit for vasculitis and renal disease.

# The Evolution of Highly Effective Treatment

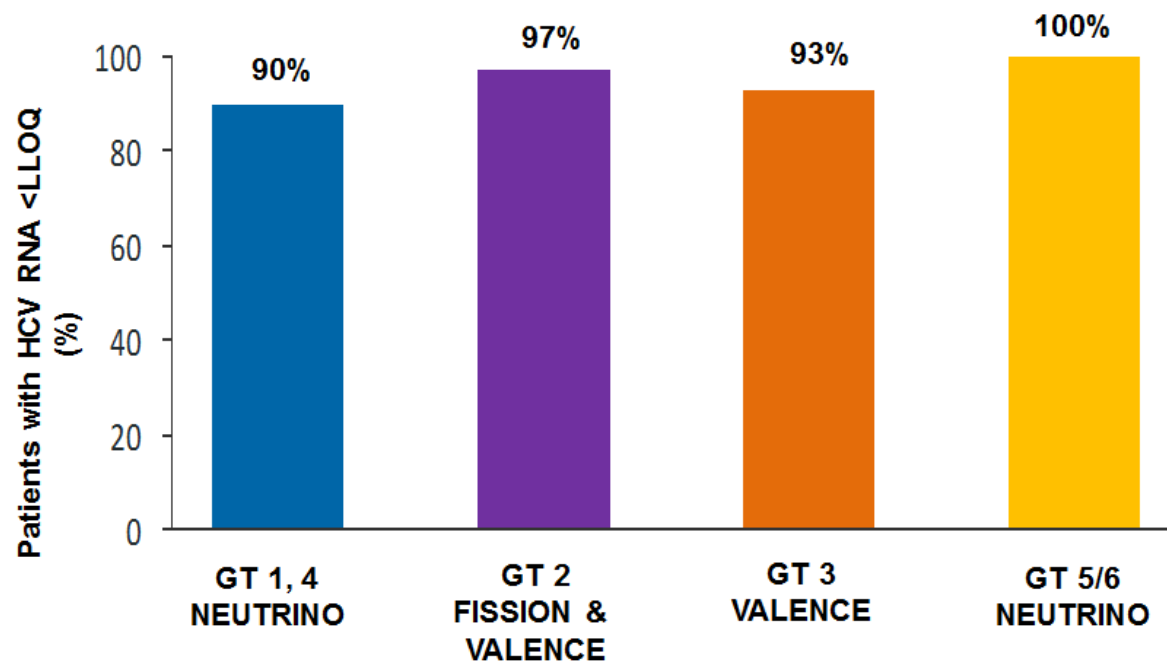


*Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.*

# Sofosbuvir

- NS5B polymerase inhibitor (chain terminator).
- Potent activity against genotypes 1–6.
- Once-daily, oral, 400-mg tablet.
- Safe and well tolerated.
- Priced at \$80,000 per 12 week course.

# > 90% SVR 12 Across Treatment-Naïve Genotypes 1, 2, 3, 4, 5, 6



*Lawitz E, et al. N Engl J Med. 2013 May 16.*

*Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02.*

*Zeuzem S, et al. AASLD 2013. Washington, DC. #1085.*

# The Holy Grail of HCV Therapy: Interferon Free

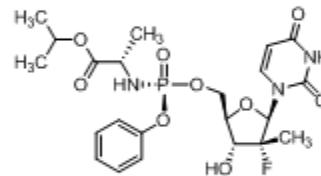
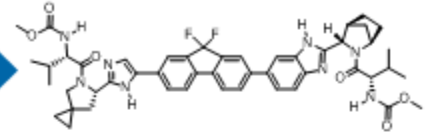


# Ledipasvir/Sofosbuvir: A Single Tablet Regimen (STR)

- Approval Status: FDA approved October 10, 2014.
- Dosing: One tablet (fixed dose 90 mg ledipasvir/400 mg sofosbuvir) orally once daily with or without food.
- Wholesale Acquisition Cost in United States: \$1125 per pill:
  - 8-week course = \$63,000
  - 12-week course = \$94,500
  - 24-week course = \$189,000

*Source: Harvoni Prescribing Information. Gilead Sciences*

LDV  
NS5A  
inhibitor



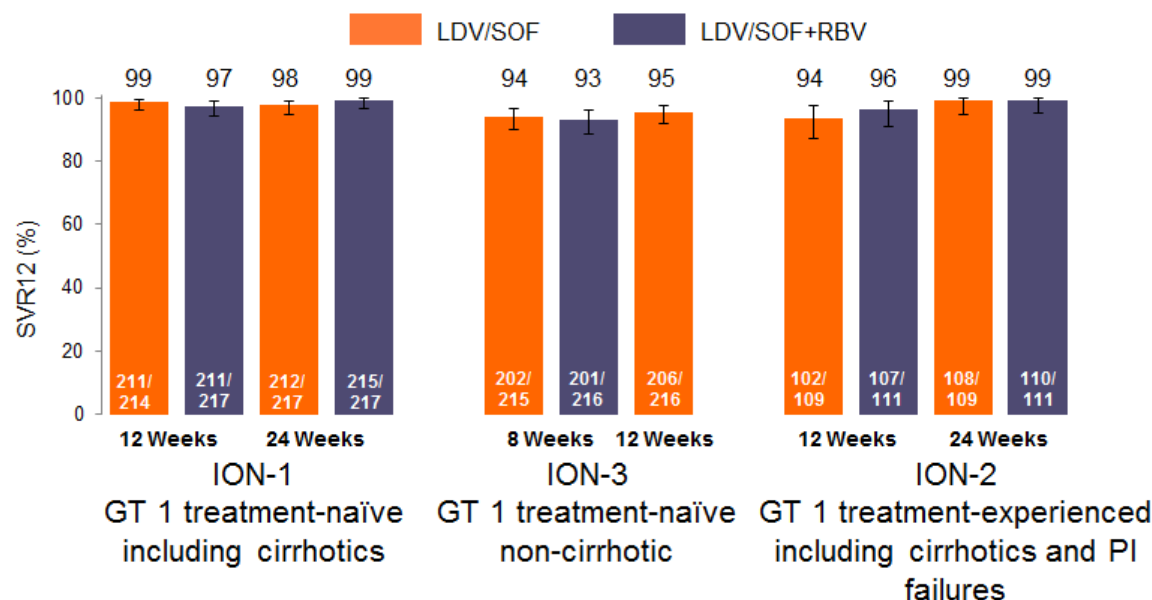
SOF - NS5B  
nucleotide  
polymerase  
inhibitor

LDV  
NS5A  
inhibitor

SOF - NS5B  
nucleotide  
polymerase  
inhibitor

# ION Phase 3 Program (ION-1, ION-2, ION-3)

## Efficacy Summary



- 97% (1886/1952) overall SVR rate

Error bars represent 95% confidence intervals.

Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print].

Kowdley K, et al. *N Engl J Med* 2014; 2014 Apr 11 [Epub ahead of print].

Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print].

# Ledipasvir-Sofosbuvir (Harvoni)

## Indications and Usage

Genotype 1 Patient Populations	Treatment Duration*
Treatment naïve with or without cirrhosis.	12 weeks
Treatment experienced** without cirrhosis.	12 weeks
Treatment experienced** with cirrhosis	24 weeks

\*Consider treatment duration of eight weeks in treatment-naïve patients without cirrhosis who have a pretreatment HCV RNA less than 6 million UI/mL.

\*\*Treatment-experienced patients who have failed treatment with either of the following:

- Peginterferon alfa plus ribavirin.
- HCV protease inhibitor plus peginterferon alfa plus ribavirin.

*Source: Harvoni Prescribing Information. Gilead Sciences.*

# Who should be treated for HCV?

- Persons with chronic HCV infection.

# Highest Priority for Treatment: Highest Risk of Severe Complications

- Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4).
- Organ transplant.
- Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis).
- Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis.

<http://hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy>

# High Priority: High Risk for Complications

- Fibrosis (Metavir F2).
- HIV-1 coinfection.
- HBV coinfection.
- Other coexistent liver disease (eg, NASH).
- Debilitating fatigue.
- Type 2 Diabetes mellitus.
- Porphyria cutanea tarda.

<http://hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy>

# Staging Hepatitis C

- Invasive:
  - Liver biopsy (Gold Standard historically).
- Non Invasive:
  - Fibroscan.
- Laboratory markers:
  - AST Platelet Ratio Index (APRI).
  - FIB-4 Index.
  - Fibrosure.

Metavir Liver Biopsy Score

Fibrosis	Score
No fibrosis	0
Portal fibrosis w/o septa	1
Few septa	2
Numerous septa w/o cirrhosis	3
Cirrhosis	4

# APRI Calculator

Clinical Calculators - Hepatitis C Online

**Hepatitis C Online**

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[HCV Medications](#) [Course Modules](#) [Slide Lectures](#) [Core Concepts](#) [Master Bibliography](#) **Clinical Calculators** [Search](#)

**Clinical Calculators**

- APRI Calculator**
- AUDIT-C Questionnaire
- BMI Calculator
- CrCl Calculator
- CAGE Questionnaire
- CTP Calculator
- FIB-4 Calculator
- Glasgow Coma Scale
- MDRD GFR Calculator
- MELD Calculator
- SAAG Calculator

### AST to Platelet Ratio Index (APRI) Calculator

This is an AST to Platelet Ratio Index calculator tool. Enter the required values to calculate the APRI value. The APRI Score will appear in the oval on the far right (highlighted in yellow). Most laboratories use 40 IU/L as the value for the AST upper limit of normal.

AST Level (IU/L)

0

AST (Upper Limit of Normal) (IU/L)

0

Platelet Count (10<sup>9</sup>/L)

0

**APRI =****x 100 =**

**Interpretation:**

In a meta-analysis of 40 studies, investigators concluded that an APRI cutoff of 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. Similarly, an APRI cutoff of 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis.

Source: Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology*. 2011;53:726-36.

Funded by a grant from the  
Centers for Disease Control and  
Prevention

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IAS-USA  
International Antiviral Society-USA

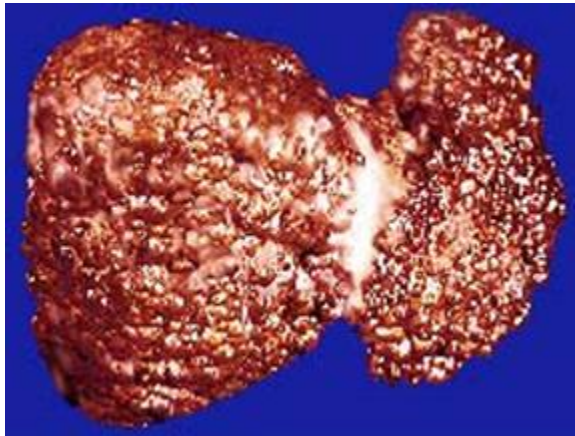
# Why Treat HCV Now?

- The costs for HCV are significantly higher for those with more severe disease.
- Chronic HCV infection increases mortality.
- Those who achieve SVR see a reduction in HCV morbidity and mortality.
- SVR rates are higher in patients with milder vs more advanced disease.

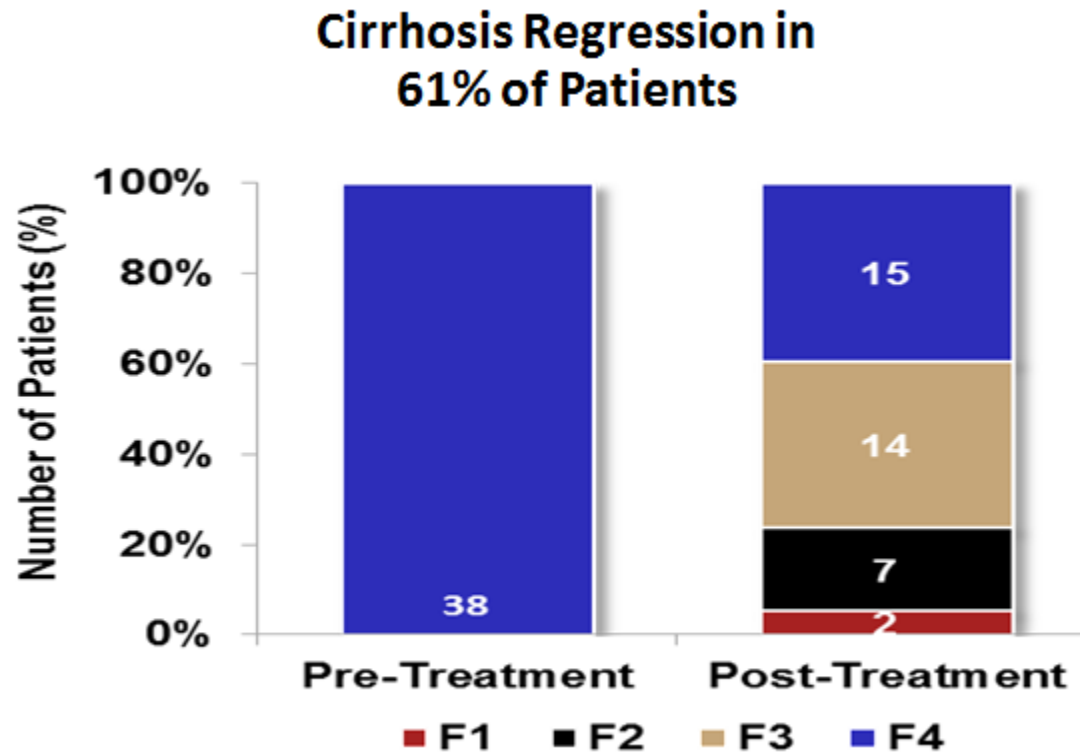
# What do we get with HCV Treatment?

- SVR (cure) of HCV is associated with:
  - 70% Reduction of Liver Cancer.
  - 50% Reduction in All-cause Mortality.
  - 90% Reduction in Liver Failure.

Lok A. NEJM 2012; Ghany M. Hepatol 2009; Van der Meer AJ. JAMA 2012

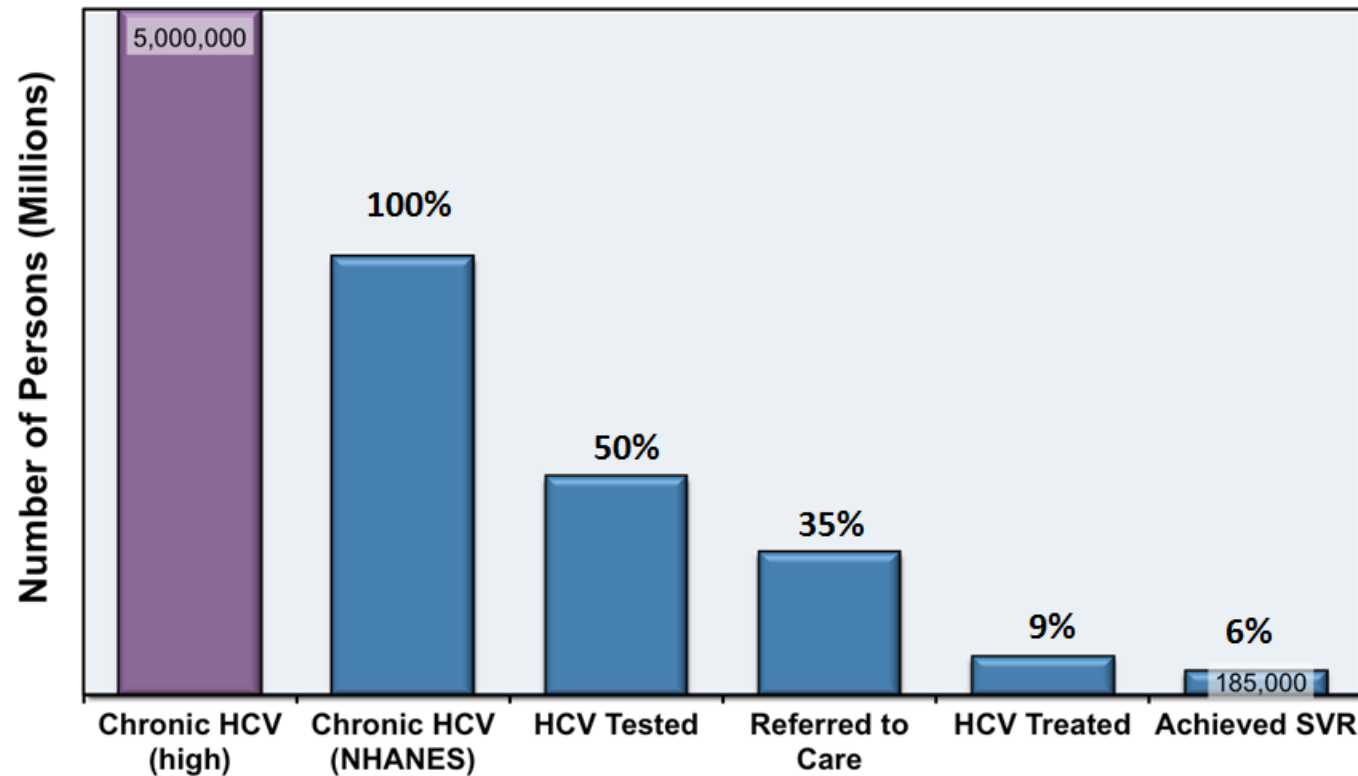


# Cirrhosis Regression and Fibrosis Reduction Following SVR



*D'Ambrosio R, et al. Hepatology. 2012;56:532-543*

# Hepatitis C Cascade of Care in United States



Source: Holmberg SD, et al. *N Engl J Med.* 2013;368:1859-61.

# Role of the Primary Care Clinician in HCV

- Screening for HCV.
- Counseling on modifiable risk factors important in disease progression (weight loss, diabetes control, alcohol, marijuana).
- Staging of liver disease.
- Recognition of extra-hepatic manifestations.
- Treatment (with mentoring) or linkage to someone who treats HCV.

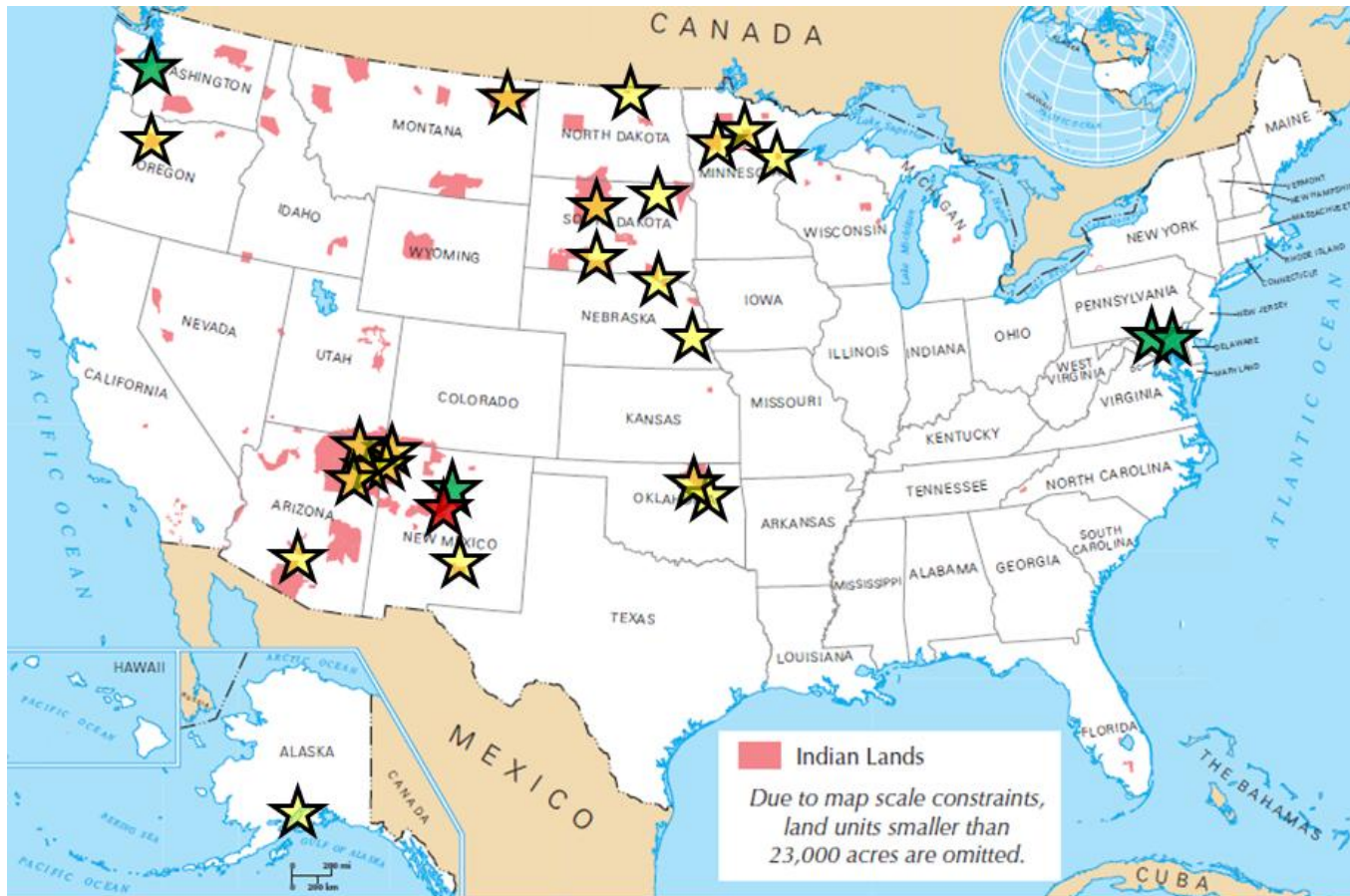
# Project ECHO



# IHS HCV Clinic



# IHS HCV ECHO Participating Sites



★ Project ECHO

Map: [nationalatlas.gov](http://nationalatlas.gov)

# Opportunities for Mentoring and Treatment through Telehealth

- UNM ECHO (Albuquerque).
- UW ECHO (Seattle).
- Arizona ECHO (Phoenix, St. Joseph's).
- University of Utah ECHO (Salt Lake City).
- Baylor ECHO (Houston).
- ANTHC (AK facilities).

# Opportunities for Mentoring and Treatment through Telehealth (cont.)

- ECHO provides CMEs for attendance, even if not treating patients.
- CPEs also available at ABQ ECHO sessions.

# Cost Issues and Drug Access

- Over \$1000 per pill.
- Many state Medicaid and insurance programs limiting access.
- Patient Assistance Programs (PAPs).
- Paperwork required but gets quicker with experience.
- IHS success with PAPs excellent so far.
- Webinar devoted to PAPs including templates for forms and letters is scheduled for IHS.

# Final Thoughts

- The HCV Epidemic is upon us:
  - 3 to 5 million chronically infected.
  - Rapidly rising liver-related mortality.
- Testing and linkage to care are needed:
  - Still only 25% - 50% estimated diagnosed.
  - Limited number of providers familiar with HCV treatment (Project ECHO).
- HCV treatments are improving rapidly:
  - Costs may be prohibitive to allow equitable access.
  - Complex medical and societal issue.

# Slide Acknowledgments

- Christian B. Ramers, MD, MPH/CDC.
- CDC/University of Washington's online HCV curriculum <http://hepatitisc.uw.edu/>.
- Paulina Deming, PharmD.
- Jorge Mera, MD.
- Gilead.

Questions?